page 9, line 26; page 10, lines 16-24; page 18, lines 2-3; and page 18, line 8 and in originally-filed claims 16 and 18. Applicants respectfully request entry of the foregoing amendments and submit that no new matter is introduced by the amendments.

Rejections under 35 U.S.C. § 112, Second Paragraph

Claims 45-64 and 66-84 were rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particular point out and distinctly claim the subject matter that the Applicants regard as the invention.

Specifically, claim 45 was rejected under 35 U.S.C. § 112, second paragraph, because it lacks a correlating step at the end to accomplish the preamble. Claim 45 is amended to recite, in part, that the comparing step allows for determination of an activity of one or more components of the Protein C anticoagulant pathway. Support for the amendment is found in the Specification on, for example, page 10, lines 16-24.

Claim 46 was rejected under 35 U.S.C. § 112, second paragraph, for failing to further limit claim 45 from which it depends because claim 45 does not contain the Mg^{+2} ion in step (d). Step (d) of claim 45 has been amended to include the Mg^{+2} ion. Support for the amendment is found in the Specification on, for example, page 10, lines 16-24.

Claim 63 was rejected under 35 U.S.C. § 112, second paragraph, for containing a typographical error. Claim 63 has been amended to remove the repetition of "selected from the group consisting."

Claim 70 was rejected under 35 U.S.C. § 112, second paragraph, for containing improper Markush terminology. Claim 70 has been amended to recite, "at least one component selected from the group consisting of..."

In light of the foregoing, Applicants respectfully request reconsideration and withdrawal of all of the rejections under 35 U.S.C. § 112, second paragraph.

Rejection under 37 C.F.R. 1.75(c)

Claim 65 was objected under 37 C.F.R. 1.75(c) as being in improper form because a multiple dependent claim must be in the alternative. Claim 65 has been amended to recite, "The method as in any one of claims 59-61..." Accordingly, Applicants respectfully request reconsideration and withdrawal of this objection.

Double Patenting

Applicants acknowledge the rejection of claims 45-64 and 66-84 under the judicially created doctrine of obviousness-type double patenting over claims 1-50 of U.S. Patent No. 6,395,501. Applicants request that this rejection be held in abeyance until such time as the claims in the present application are otherwise allowable.

Furthermore, Applicants would like to make the Examiner aware of U.S. Serial No. 10/331,731 (filed December 30, 2002), which is related to the present application. Applicants note that the claims of U.S. Serial No. 10/331,731 are similar to those issued in parent U.S. Patent No. 6,395,501. A copy of the application is presented herein for consideration by the Examiner.

Respectfully submitted,

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MARKED-UP VERSION OF AMENDMENT TO SPECIFICATION

On page 56, in the title of the Abstract, please amend the title to read as follows.

IN VITRO METHODS[, REAGENTS AND KITS] FOR SCREENING FOR BLOOD COAGULATION DISORDERS USING METAL IONS

MARKED-UP VERSION OF CHANGES TO CLAIMS

45. (Amended) An in vitro method for determining the functional activity of one or more components of the Protein C anticoagulant pathway of the blood coagulation system, comprising:

(a) providing a blood sample to be analyzed;

(b) activating the coagulation cascade by adding a procoagulant reagent to the blood sample to be analyzed;

(c) triggering coagulation by adding calcium ions to the blood sample;

(d) adding metal ions selected from the group consisting of Mg^{+2}, Mn^{+2}, Zn^{+2}, Ni^{+2}, Sr^{+2}, Cu^{+2}, or Cu^{+}, ions at a concentration that increases the anticoagulant activity of one or more components of the Protein C anticoagulant pathway;

(e) incubating a reaction mixture comprising the components recited in steps (a)-(d);

(f) observing clotting time; and

(g) comparing the clotting time for the blood sample to be analyzed with the clotting time for a normal blood sample as determined by the method recited in steps (a)-(f), thereby allowing for determination of an activity of one or more components of the Protein C anticoagulant pathway.

46. (Amended) The method according to claim 45, wherein the metal ion [is]comprises Mg^{2+}.

47. (Amended) The method according to claim 46, wherein the metal ion comprises Mg^{2+} and the amount of the Mg^{2+} ions added in step (d) is about 20 µmol to 10 mmol per liter of reaction mixture.

48. (Amended) The method according to claim 46, wherein the metal ion comprises Mg^{2+} and the amount of the Mg^{2+} ions added in step (d) is about 100 µmol to 2 mmol per liter of reaction mixture.

49. (Amended) The method according to claim 46, wherein the metal ion comprises Mg^{2+} and the amount of the Mg^{2+} ions added in step (d) is about 200 μmol to 1 mmol per liter of reaction mixture.

59. (Amended) The method according to claim[s] 45, wherein the activating the coagulation cascade step occurs via the intrinsic pathway and the [coagulation activator for the intrinsic pathway compositions]procoagulation reagent comprises at least one phospholipid[(s)] and at least one contact activator[s].

60. (Amended) The method according to claim 45, wherein the activating the coagulation cascade step occurs via the intrinsic pathway and the [coagulation activator]procoagulation reagent comprises at least one phospholipid[s] and [an]at least one intrinsic pathway factor selected from the group consisting of Factor IXa, Factor XIIa, and Factor XIa.

61. (Amended) The method according to claim 45, wherein the activating the coagulation cascade step occurs via the intrinsic pathway [and the coagulation activator]and the [coagulation activator]procoagulation reagent comprises at least one phospholipid, at least one contact activator and [an]at least one intrinsic pathway factor selected from the group consisting of Factor[s] IXa, Factor XIIa, and Factor XIa.

62. (Amended) The method according to claim [59]61, wherein the at least one contact activator is selected from the group consisting of ellagic acid, collagen, collagen-related substances, and silica.

63. (Amended) The method according to claim 62, wherein the at least one contact activator is a silica [selected from the group consisting]selected from the group consisting of micronized silica, colloidal silica, and kaolin.

64. (Amended) The method according to claim 45, wherein the activating the coagulation cascade step occurs via the extrinsic pathway and the [coagulation activator for the extrinsic pathway is]procoagulation reagent comprises a material selected from the group consisting of native human tissue factor, recombinant human tissue factor, non-human native tissue factor, non-human recombinant tissue factor, native human Factor VII/VIIa, recombinant human Factor VII/VIIa, native non-human Factor VII/VIIa, and recombinant non-human Factor VII/VIIa.

65. (Amended) The method as in [according to] any one of claims [59-60]59-61, wherein the at least one phospholipid[s are] is selected from the group consisting of synthetic phospholipids, purified phospholipids, and crude extracts of phospholipids derived from biological sources.

66. (Amended) The method according to claim [66]65, wherein the at least one phospholipid[s are] is selected from the group consisting of phosphatidylcholine, phosphatidylserine, and [sphinogmyelin]sphingomyelin.

67. (Amended) The method according to claim 45, wherein the activating the coagulation cascade step occurs via the common pathway and the [coagulation activator is]procoagulation reagent comprises a material selected from the group consisting of exogenous Factor Xa, exogenous Factor X and an exogenous activator for Factor X, and an exogenous activator for endogenous Factor X.

68. (Amended) The method according to claim 67, wherein the exogenous activator for Factor X [is]comprises snake venom enzyme.

70. (Amended) The method according to claim 45, further comprising the step of adding at least one component[s] [of the Protein C anticoagulant pathway to compensate for variable functional levels of the components of the anticoagulant pathway in the sample, said components being] selected from the group consisting of Protein C, activated Protein C, Protein S, Factor V, Factor Va, a plasma deficient of the Protein C anticoagulant pathway component to be analyzed, and a plasma deficient of all components of the Protein C anticoagulant pathway.

71. (Amended) The method according to claim 45, [further comprising the step of adding]wherein a fibrin polymerization inhibitor is added to the blood sample to be analyzed.

73. (Amended) The method according to claim 45, wherein the procoagulation reagent [is]comprises a material selected from the group consisting of Factor VIII, Factor VIIIa, Factor IX, Factor X, and prothrombin.

74. (Amended) The method [of]according to claim 45, [wherein the component of the Protein C anticoagulant pathway analyzed is Protein C, said]the method further comprising the step of providing [activating]activated Protein C by adding exogenous activated Protein C to the blood sample to be analyzed.

75. (Amended) The method according to claim 45, [wherein the component of the Protein C anticoagulant pathway analyzed is Protein C, said]the method further comprising the step of [activating]providing activated Protein C by adding an activator of Protein C to the blood sample to be analyzed.

76. (Amended) The method according to claim 45, [wherein the component of the Protein C anticoagulant pathway analyzed is Protein C, said]the method further comprising the step of providing activated Protein C by adding exogenous Protein C together with an activator of Protein C to the blood sample to be analyzed.

77. (Amended) The method as in [according to] any one of claims [45]74-76, wherein the adding metal ions [are added]step occurs simultaneously with the providing activated Protein C [activator]step.

78. (Amended) The method as in [according to] any one of claims [45]74-76, wherein the providing [activating]activated Protein C step occurs simultaneously with the activating the coagulation cascade step.

79. (Amended) The method as in [according to] any one of claims [45]74-76, wherein the providing [activating]activated Protein C step precedes the activating the coagulation cascade step.

80. (Amended) The method as in [according to] any one of claims [45]74-76, wherein the[activator for] Protein C activator comprises at least one substance selected from the group consisting of Protein C activating snake venom enzyme and thrombin.

81. (Amended) The method as in [according to] any one of claims [45]74-76, wherein the [activator for]Protein C activator comprises thrombomodulin.

82. (Amended) The method as in [according to] any one of claims [80]74-76, wherein the Protein C activator [is]comprises recombinant Protein C activator.

83. (Amended) The method according to claim [82]80, wherein the Protein C activating snake venom enzyme is obtained from the Agkistrodon family[of Agkistrodon contortrix contortrix].

85. (New) The method according to claim 83, wherein the snake venom enzyme is obtained from Agkistrodon contortrix contortrix.

86. (New) The method according to claim 83, wherein the snake venom enzyme comprises crude snake venom enzyme.

87. (New) The method according to claim 83, wherein the snake venom enzyme comprises purified snake venom enzyme.

88. (New) The method according to claim 87, wherein the amount of purified snake venom enzyme is about $1x10^{-3}$ U to 1 U per milliliter of reaction mixture.

89. (New) The method according to claim 87, wherein the amount of purified snake venom enzyme added is about $2x10^{-3}$ U to .3 U per milliliter of reaction mixture.